

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 31 May 2001 (31.05.01)	
International application No. PCT/EP00/09722	Applicant's or agent's file reference PI3806
International filing date (day/month/year) 05 October 2000 (05.10.00)	Priority date (day/month/year) 07 October 1999 (07.10.99)
Applicant ALVARO, Giuseppe et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 April 2001 (17.04.01)
☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
 34, chemin des Colombettes
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Cécile Chatel (Fax 338.87.40)

Telephone No.: (41-22) 338.83.38

EP0009722

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

FILLER, Wendy, Anne
GlaxoSmithKline
Corporate Intellectual Property
(CN9.25.1)
980 Great West Road
Brentford
Middlesex TW8 9GS
ROYAUME-UNI

Date of mailing (day/month/year) 07 February 2002 (07.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference PI3806	
International application No. PCT/EP00/09722	International filing date (day/month/year) 05 October 2000 (05.10.00)

1. The following indications appeared on record concerning:
- ☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address FILLER, Wendy, Anne GlaxoSmithKline Corporate Intellectual Property Two New Horizons Court Brentford, Middlesex TW8 9EP United Kingdom	State of Nationality	State of Residence
	Telephone No. 020 8966 8412	
	Facsimile No. 020 8966 8838	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:
- ☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address FILLER, Wendy, Anne GlaxoSmithKline Corporate Intellectual Property (CN9.25.1) 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom	State of Nationality	State of Residence
	Telephone No. +44 20 8047 5000	
	Facsimile No. +44 20 8047 6894	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

- ☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Jean-Luc MARTIN
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

004649681

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
GLAXO WELLCOME PLC
Glaxo Wellcome House
Attn. Filler, Wendy Anne
Berkeley Avenue
Greenford
Middlesex UB6 0NN
UNITED KINGDOM

Global

RECEIVED

23 APR 2001

ACTION
DATE

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing:
(day/month/year)

20/04/2001

Applicant's or agent's file reference

PI3806

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 00/09722

International filing date
(day/month/year)

05/10/2000

Applicant

GLAXO GROUP LIMITED et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

John De Bruijn

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims...

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
GLAXO WELLCOME PLC
Glaxo Wellcome House
Attn. Filler, Wendy Anne
Berkeley Avenue
Greenford
Middlesex UB6 0NN
UNITED KINGDOM

Global I

RECEIVED

23 APR 2001

ACTION
DATE

NOTIFICATION OF TRANSMITTAL OF
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Date of mailing:
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20/04/2001

Applicant's or agent's file reference

PI3806

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 00/09722

International filing date

(day/month/year)

05/10/2000

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4. **Further action(s):** The applicant is reminded of the following:

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European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

John De Bruijn

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NOTES TO FORM PCT/ISA/220 (continued)

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- (ii) the claim is cancelled;
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- (iv) the claim replaces one or more claims as filed;
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2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

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It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

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Consequence with regard to translation of the international application for entry into the national phase

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For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PI3806	FOR FURTHER ACTION		see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/EP 00/09722	International filing date (day/month/year) 05/10/2000	(Earliest) Priority Date (day/month/year) 07/10/1999	
Applicant GLAXO GROUP LIMITED et al.			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PIPERAZINE COMPOUNDS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

CT/EP 00/09722

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D	1,15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

4 April 2001

Date of mailing of the international search report

20/04/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/09722

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/09722

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4308387	A	29-12-1981	AT 380685 B	25-06-1986
			AT 219383 A	15-11-1985
			AT 376666 B	27-12-1984
			AT 683479 A	15-05-1984
			AU 529260 B	02-06-1983
			AU 5198479 A	19-06-1980
			BE 879528 A	21-04-1980
			CA 1130807 A	31-08-1982
			CH 643247 A	30-05-1984
			DE 2941880 A	30-04-1980
			DK 442779 A,B,	21-04-1980
			ES 485188 A	16-05-1980
			FI 793238 A,B,	21-04-1980
			FR 2439187 A	16-05-1980
			GB 2037745 A,B	16-07-1980
			HK 57184 A	03-08-1984
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			JP 1482061 C	27-02-1989
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			LU 81807 A	25-01-1980
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			NZ 191867 A	14-06-1983
			SE 448730 B	16-03-1987
			SE 7908701 A	21-04-1980
			SG 7384 G	08-02-1985
			US 4385057 A	24-05-1983
			US 4447433 A	08-05-1984

PCT REQUEST

1/5

EPA EPO-OEB DG 1 Requ:	
05. 10. 2000	
11	ANL. ZEICHN.

PI3806

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

0	Form receiving Office used only	
0-1	International Application No.	PCT/EP 00 / 09722
0-2	International Filing Date	05 OCT 2000 (05. 10. 00)
0-3	Name of receiving Office and "PCT International Application"	EUROPEAN PATENT OFFICE PCT INTERNATIONAL APPLICATION
0-4	Form - PCT/RO/101 PCT Request Prepared using	PCT-EASY Version 2.91 (updated 01.07.2000)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	PI3806
I	Title of invention	CHEMICAL COMPOUNDS
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	GLAXO GROUP LIMITED
II-5	Address:	GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD, Middlesex UB6 0NN United Kingdom
II-6	State of nationality	GB
II-7	State of residence	GB
II-8	Telephone No.	020 8966 8000
II-9	Facsimile No.	020 8966 8838
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	ALVARO, Giuseppe
III-1-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-1-6	State of nationality	IT
III-1-7	State of residence	IT

PCT REQUEST

PI3806

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	DI FABIO, Romano
III-2-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-2-6	State of nationality	IT
III-2-7	State of residence	IT
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	GIOVANNINI, Riccardo
III-3-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-3-6	State of nationality	IT
III-3-7	State of residence	IT
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	GUERCIO, Giuseppe
III-4-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-4-6	State of nationality	IT
III-4-7	State of residence	IT
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	ST-DENIS, Yves
III-5-5	Address:	Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-5-6	State of nationality	CA
III-5-7	State of residence	IT

PCT REQUEST

PI3806

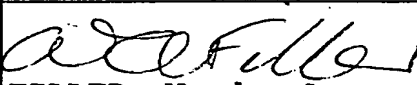
Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

III-6	Applicant and/ r invent r	applicant and inventor US only URSINI, Antonella Glaxo Wellcome SpA Via Alessandro Fleming 2 I-37135 Verona Italy
III-6-1	This person is:	
III-6-2	Applicant for	
III-6-4	Name (LAST, First)	
III-6-5	Address:	
III-6-6	State of nationality	IT
III-6-7	State of residence	IT
IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent FILLER, Wendy, Anne Glaxo Wellcome plc Glaxo Wellcome House Berkeley Avenue Greenford, Middlesex UB6 ONN United Kingdom 020 8966 8000 020 8966 8838
IV-1-1	Name (LAST, First)	
IV-1-2	Address:	
IV-1-3	Telephone No.	
IV-1-4	Facsimile No.	
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE ^{TR} and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

PCT REQUEST

PI3806

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V-5	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-6 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.		
V-6	Exclusion(s) from precautionary designations	NONE	
VI-1	Priority claim of earlier national application		
VI-1-1	Filing date	07 October 1999 (07.10.1999)	
VI-1-2	Number	9923748.9	
VI-1-3	Country	GB	
VII-1	International Searching Authority Chosen	European Patent Office (EPO) (ISA/EP)	
VIII	Check list	number of sheets	electronic file(s) attached
VIII-1	Request	5	-
VIII-2	Description	96	-
VIII-3	Claims	6	-
VIII-4	Abstract	2	pi3806-cab.txt
VIII-5	Drawings	0	-
VIII-7	TOTAL	109	
	Accompanying items	paper document(s) attached	electronic file(s) attached
VIII-8	Fee calculation sheet	✓	-
VIII-9	Separate signed power of attorney	✓	-
VIII-12	Priority document(s)	Item(s) VI-1	-
VIII-16	PCT-EASY diskette	-	diskette
VIII-18	Figure of the drawings which should accompany the abstract		
VIII-19	Language of filing of the international application	English	
IX-1	Signature of applicant or agent		
IX-1-1	Name (LAST, First)	FILLER, Wendy, Anne	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	05 OCT 2000	(05.10.00)
10-2	Drawings:		
10-2-1	Received		
10-2-2	Not received		

PCT REQUEST

PI3806

Original (for SUBMISSION) - printed on 29.09.2000 03:07:51 PM

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
------	--	--

PATENT COOPERATION TREATY

From the RECEIVING OFFICE

PCT

To:

Filler, Wendy Anne
GLAXO WELLCOME PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
GRANDE BRETAGNE

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

07 11 2000

Applicant's or agent's file reference

PI3806

IMPORTANT NOTIFICATION

International application No.

PCT/EP 00/ 09722

International filing date (day/month/year)

05/10/2000

Priority date (day/month/year)

07/10/1999

Applicant

GLAXO GROUP LIMITED

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.
3. ☐ Other:

Global Intellectual Property	
RECEIVED <div style="text-align: center; font-size: 1.2em; font-weight: bold;">10 NOV 2000</div>	INIT <div style="text-align: center; font-size: 1.2em;">HU</div>
<div style="text-align: center; font-size: 1.2em;">Dmk</div>	FILE <div style="text-align: center; font-size: 1.2em;">Dmc</div>

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the receiving Office



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

R.L.R. PETHER

Form PCT/RO:105 (0792) P20402

Express Mail Label No.:

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

CORPORATE INTELLECTUAL PROPERTY	
Received	15 GEN 2002
VERONA	File PCT

To:

Filler, Wendy Anne
GLAXO WELLCOME PLC
Glaxo Wellcome House
Berkeley Avenue
Greenford
Middlesex UB6 0NN
GRANDE BRETAGNE

Corporate Intellectual Property	
RECEIVED	INT
- 7 JAN 2002	
Action Date	ATTN

**NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**
(PCT Rule 71.1)

Date of mailing (day/month/year) 03.01.2002

Applicant's or agent's file reference
PI3806

IMPORTANT NOTIFICATION

International application No. PCT/EP00/09722	International filing date (day/month/year) 05/10/2000	Priority date (day/month/year) 07/10/1999
---	--	--

Applicant
GLAXO GROUP LIMITED et al.

09 JAN 2002

DV

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

Ambroa, J.R.

Tel. +49 89 2399-8012



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PI3806	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/09722	International filing date (day/month/year) 05/10/2000	Priority date (day/month/year) 07/10/1999
International Patent Classification (IPC) or national classification and IPC C07D241/04		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17/04/2001	Date of completion of this report 03.01.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schuemacher, A Telephone No. +49 89 2399 7818



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09722

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
Description, pages:

1-96 as originally filed

Claims, No.:

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/09722

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 18.

because:

- ☒ the said international application, or the said claims Nos. 18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims
	No: Claims 1-19
Inventive step (IS)	Yes: Claims
	No: Claims 1-19
Industrial applicability (IA)	Yes: Claims 1-17, 19

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09722

No: Claims

2. Citations and explanations
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:US-A-4 308 387 (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29)

D2:DAVID T. DAVIES: 'SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES' JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820

Reference is also made to the letter of the Applicant dated the 1st of November 2001 and to document D3:

D3: WO 97/36593 A (MERCK & Co.) 9 October 1997

1. Novelty, Article 33(2) PCT:

The present application discloses piperazine compounds, which are potent and specific antagonists of tachykinins, processes for their preparation and the pharmaceutical compositions containing them.

Document D1 describes diphenylbutyl-piperazinecarboxamides, from which the subject-matter of claim 1 differs mainly in that the substituent R₄ in formula (I) cannot be a diphenylbutyl-substituent.

Document D2 discloses piperazine-2,3-diones, which differ from the compounds of claim 1 because of the presence of the carbonyl group in position 3.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

The Applicant cites document 3 in which inhibitors of farnesyl-protein transferase are disclosed. These compounds can have the same formula as the present claimed compounds (see in D3, claim 1, W is a heterocycle, $p=0$, X is CO, s is 0, G is H_2 and R^2 or R^3 can be an aryl ring substituted with one or more fluorine). Even if the Applicant has disclaimed these particular compounds (when R^1 and R^2 form a heterocycle, then m is 1 or 2 and R is not fluorine) he should also disclaim in order to meet the requirements for novelty the case, when R^1 and R^2 form a heterocycle and m is 3, then R must not be fluorine, otherwise the subject-matter of claim 1-17 and 19 can not be considered as new (Art. 33(2), PCT).

2. Inventive step, Article 33(3) PCT:

The problem to be solved by the present invention may be regarded as to find piperazine derivatives, which are potent and specific antagonists of tachykinins.

The document D1 is regarded as being the closest prior art to the subject-matter of the present application, and shows diphenylbutyl-piperazinecarboxamides, which differ from the compounds of claim 1 because of the diphenylbutyl-substituent on the nitrogen atom of the piperazine ring.

The examining division agrees with the Applicant, that there is no prediction or suggestion in D1, that this diphenylbutyl substituent borne by the nitrogen-atom of the piperazine ring could be interchanged with other substituent defined as R_4 in the present application; therefore the subject-matter of claim 1 could be regarded as involving an inventive step.

However, it should be pointed out that it must be made credible that essentially all of the claimed matter solves the given problem and that only the compounds which are suitable for solving the problem underlying the present subject-matter could be claimed.

Now in the description, the compounds tested for their affinity for NK1 receptor are those where R_4 is almost always hydrogen, R_5 is always methyl or hydrogen and R_3 is always CF_3 ($n=2$) and therefore, the scope of the claim 1 seems to be too broad and not supported by the description.

Consequently, claim 1 as well as dependant compounds-claims 2-15, claims 16 and 17 concerning the use and the pharmaceutical composition containing such compounds and the process for their preparation disclosed in claim 19 do not meet the requirements of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

Article 33(2) and 33(3) PCT.

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:

FILLER, Wendy, Anne
Glaxo Wellcome plc
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
ROYAUME-UNI Intellectual Property

20 APR 2001

Date of mailing (day/month/year) 12 April 2001 (12.04.01)		
Applicant's or agent's file reference P13806/PCT		IMPORTANT NOTICE <i>DMC JMC</i>
International application No. PCT/EP00/09722	International filing date (day/month/year) 05 October 2000 (05.10.00)	Priority date (day/month/year) 07 October 1999 (07.10.99)
Applicant GLAXO GROUP LIMITED et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EA, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU,
The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 12 April 2001 (12.04.01) under No. WO 01/25219

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colmbettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer J. Zahra Telephone No. (41-22) 338.83.38
---	---

INTERNET COOPERATION TREATY
RECEIVED

PCT

20 AUG 2001 From the INTERNATIONAL BUREAU

NEW HORIZONS COURT

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

Corporate Intellectual Property

RECEIVED

INIT

FILLER, Wendy, Anne
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP
ROYAUME-UNI

20 AUG 2001

FILE

Date of mailing (day/month/year)
08 August 2001 (08.08.01)

Applicant's or agent's file reference
PI3806 / PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP00/09722

International filing date (day/month/year)
05 October 2000 (05.10.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address

FILLER, Wendy, Anne
Glaxo Wellcome plc
Glaxo Wellcome House
Berkeley Avenue
Greenford, Middlesex UB6 0NN
United Kingdom

State of Nationality

State of Residence

Telephone No.

020 8966 8000

Facsimile No.

020 8966 8838

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

FILLER, Wendy, Anne
GlaxoSmithKline
Corporate Intellectual Property
Two New Horizons Court
Brentford, Middlesex TW8 9EP
United Kingdom

State of Nationality

State of Residence

Telephone No.

020 8966 8412

Facsimile No.

020 8966 8838

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☐ the International Searching Authority ☒ the elected Offices concerned
☒ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

A. Karkachi

Telephone No.: (41-22) 338.83.38

REC'D 07 JAN 2002

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

12

Applicant's or agent's file reference PI3806	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP00/09722	International filing date (day/month/year) 05/10/2000	Priority date (day/month/year) 07/10/1999
International Patent Classification (IPC) or national classification and IPC C07D241/04		
Applicant GLAXO GROUP LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 7 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 17/04/2001	Date of completion of this report 03.01.2002
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schuemacher, A Telephone No. +49 89 2399 7818 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09722

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)

Description, pages:

1-96 as originally filed

Claims, No.:

1-19 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
 - ☐ the claims, Nos.:
 - ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09722

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 18.

because:

- ☒ the said international application, or the said claims Nos. 18 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims
	No: Claims 1-19
Inventive step (IS)	Yes: Claims
	No: Claims 1-19
Industrial applicability (IA)	Yes: Claims 1-17, 19

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP00/09722

No: Claims

2. Citations and explanations
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:US-A-4 308 387 (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29)

D2:DAVID T. DAVIES: 'SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES' JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820

Reference is also made to the letter of the Applicant dated the 1st of November 2001 and to document D3:

D3: WO 97/36593 A (MERCK & Co.) 9 October 1997

1. Novelty, Article 33(2) PCT:

The present application discloses piperazine compounds, which are potent and specific antagonists of tachykinins, processes for their preparation and the pharmaceutical compositions containing them.

Document D1 describes diphenylbutyl-piperazinecarboxamides, from which the subject-matter of claim 1 differs mainly in that the substituent R₄ in formula (I) cannot be a diphenylbutyl-substituent.

Document D2 discloses piperazine-2,3-diones, which differ from the compounds of claim 1 because of the presence of the carbonyl group in position 3.

The Applicant cites document 3 in which inhibitors of farnesyl-protein transferase are disclosed. These compounds can have the same formula as the present claimed compounds (see in D3, claim 1, W is a heterocycle, $p=0$, X is CO, s is 0, G is H_2 and R^2 or R^3 can be an aryl ring substituted with one or more fluorine). Even if the Applicant has disclaimed these particular compounds (when R^1 and R^2 form a heterocycle, then m is 1 or 2 and R is not fluorine) he should also disclaim in order to meet the requirements for novelty the case, when R^1 and R^2 form a heterocycle and m is 3, then R must not be fluorine, otherwise the subject-matter of claim 1-17 and 19 can not be considered as new (Art. 33(2), PCT).

2. Inventive step, Article 33(3) PCT:

The problem to be solved by the present invention may be regarded as to find piperazine derivatives, which are potent and specific antagonists of tachykinins.

The document D1 is regarded as being the closest prior art to the subject-matter of the present application, and shows diphenylbutyl-piperazinecarboxamides, which differ from the compounds of claim 1 because of the diphenylbutyl-substituent on the nitrogen atom of the piperazine ring.

The examining division agrees with the Applicant, that there is no prediction or suggestion in D1, that this diphenylbutyl substituent borne by the nitrogen-atom of the piperazine ring could be interchanged with other substituent defined as R_4 in the present application; therefore the subject-matter of claim 1 could be regarded as involving an inventive step.

However, It should be pointed out that it must be made credible that essentially all of the claimed matter solves the given problem and that only the compounds which are suitable for solving the problem underlying the present subject-matter could be claimed.

Now in the description, the compounds tested for their affinity for NK1 receptor are those where R_4 is almost always hydrogen, R_5 is always methyl or hydrogen and R_3 is always CF_3 ($n=2$) and therefore, the scope of the claim 1 seems to be too broad and not supported by the description.

Consequently, claim 1 as well as dependant compounds-claims 2-15, claims 16 and 17 concerning the use and the pharmaceutical composition containing such compounds and the process for their preparation disclosed in claim 19 do not meet the requirements of

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP00/09722

Article 33(2) and 33(3) PCT.

For the assessment of the present claim 18 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25219 A2(51) International Patent Classification⁷: C07D 241/04,
A61K 31/496, A61P 25/22[IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2,
I-37135 Verona (IT).

(21) International Application Number: PCT/EP00/09722

(74) Agent: FILLER, Wendy, Anne; Glaxo Wellcome plc,
Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex UB6 0NN (GB).

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ,
DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM,
TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(26) Publication Language: English

(30) Priority Data:
9923748.9 7 October 1999 (07.10.1999) GB(71) Applicant (*for all designated States except US*): GLAXO
GROUP LIMITED [GB/GB]; Glaxo Wellcome House,
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG,
CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

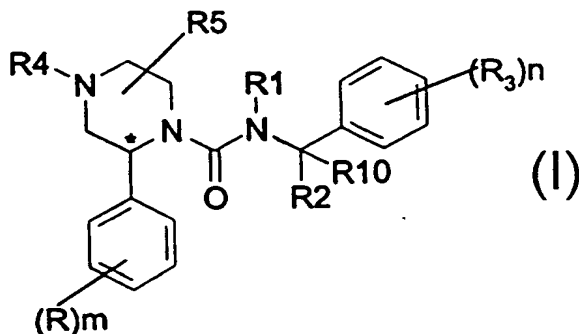
(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ALVARO, Giuseppe
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Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona
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GUERCIO, Giuseppe [IT/IT]; Glaxo Wellcome SpA, Via
Alessandro Fleming 2, I-37135 Verona (IT). ST-DENIS,
Yves [CA/IT]; Glaxo Wellcome SpA, Via Alessandro
Fleming 2, I-37135 Verona (IT). URSINI, Antonella

Published:

— Without international search report and to be republished
upon receipt of that report.For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: CHEMICAL COMPOUNDS

(57) Abstract: The present invention relates to piperazine
derivatives of formula (I) wherein R represents a halogen atom
or a C₁₋₄ alkyl group; R₁ represents hydrogen or a C₁₋₄ alkyl
group; R₂ represents hydrogen, a C₁₋₄ alkyl, C₂₋₆ alkenyl or
a C₃₋₇ cycloalkyl group; or R₁ and R₂ together with nitrogen
and carbon atom to which they are attached respectively
represent a 5-6 membered heterocyclic group; R₃ represents a
trifluoromethyl, a C₁₋₄ alkyl, a C₁₋₄ alkoxy, a trifluoromethoxy
or a halogen group; R₄ represents hydrogen, a (CH₂)_qR₇ or
a (CH₂)_rCO(CH₂)_pR₇ group; R₅ represents hydrogen, a C₁₋₄
alkyl or a COR₆ group; R₆ represents hydrogen, hydroxy,
amino, methylamino, dimethylamino a 5 membered heteroaryl
group containing 1 to 3 heteroatoms selected from oxygen,
sulphur and nitrogen or a 6 membered heteroaryl group
containing 1 to 3 nitrogen atoms; R₇ represents hydrogen,hydroxy or NR₈R₉ wherein R₈ and R₉ represent independently hydrogen or C₁₋₄ alkyl optionally substituted by hydroxy, or by
amino; R₁₀ represents hydrogen, a C₁₋₄ alkyl group or R₁₀ together with R₂ represents a C₃₋₇ cycloalkyl group; m is zero or an
integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer
from 1 to 4; provided that, when R₁ and R₂ together with nitrogen and carbon atom to which they are attached respectively represent
a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R
are not both fluorine, and pharmaceutically acceptable salts and solvates thereof.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PI3806	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 00/ 09722	International filing date (day/month/year) 05/10/2000	(Earliest) Priority Date (day/month/year) 07/10/1999
Applicant GLAXO GROUP LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PIPERAZINE COMPOUNDS

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

EP 00/09722

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D	1,15

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

4 April 2001

Date of mailing of the international search report

20/04/2001

Name and mailing address of the ISA

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 00/09722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4308387 A	29-12-1981	AT 380685 B	25-06-1986
		AT 219383 A	15-11-1985
		AT 376666 B	27-12-1984
		AT 683479 A	15-05-1984
		AU 529260 B	02-06-1983
		AU 5198479 A	19-06-1980
		BE 879528 A	21-04-1980
		CA 1130807 A	31-08-1982
		CH 643247 A	30-05-1984
		DE 2941880 A	30-04-1980
		DK 442779 A, B,	21-04-1980
		ES 485188 A	16-05-1980
		FI 793238 A, B,	21-04-1980
		FR 2439187 A	16-05-1980
		GB 2037745 A, B	16-07-1980
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		IT 1207269 B	17-05-1989
		JP 1482061 C	27-02-1989
		JP 55057572 A	28-04-1980
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		LU 81807 A	25-01-1980
		NL 7907741 A, B,	22-04-1980
		NO 793315 A, B,	22-04-1980
		NZ 191867 A	14-06-1983
		SE 448730 B	16-03-1987
		SE 7908701 A	21-04-1980
		SG 7384 G	08-02-1985
		US 4385057 A	24-05-1983
		US 4447433 A	08-05-1984

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
12 April 2001 (12.04.2001)

PCT

(10) International Publication Number
WO 01/25219 A3

(51) International Patent Classification⁷: **C07D 241/04**,
A61K 31/496, A61P 25/22, C07D 401/06, 403/06

[IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2,
I-37135 Verona (IT).

(21) International Application Number: PCT/EP00/09722

(74) Agent: **FILLER, Wendy, Anne**: GlaxoSmithKline,
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Brentford, Middlesex TW8 9EP (GB).

(22) International Filing Date: 5 October 2000 (05.10.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9923748.9 7 October 1999 (07.10.1999) GB

(71) Applicant (for all designated States except US): **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House,
Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **ALVARO, Giuseppe** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2,
I-37135 Verona (IT). **DI FABIO, Romano** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **GIOVANNINI, Riccardo** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **GUERCIO, Giuseppe** [IT/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **ST-DENIS, Yves** [CA/IT]; Glaxo Wellcome SpA, Via Alessandro Fleming 2, I-37135 Verona (IT). **URSINI, Antonella**

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

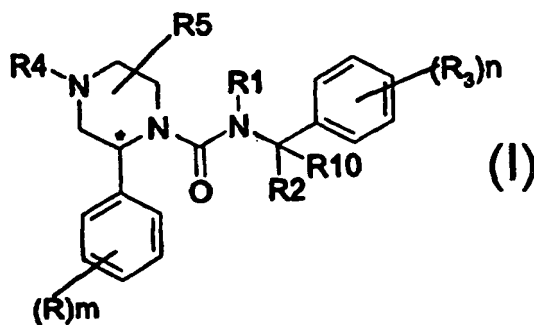
Published:

— with international search report

(88) Date of publication of the international search report:
13 December 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PIPERAZINE COMPOUNDS



(57) Abstract: The present invention relates to piperazine derivatives of formula (I) wherein R represents a halogen atom or a C₁₋₄ alkyl group; R₁ represents hydrogen or a C₁₋₄ alkyl group; R₂ represents hydrogen, a C₁₋₄ alkyl, C₂₋₆ alkenyl or a C₃₋₇ cycloalkyl group; or R₁ and R₂ together with nitrogen and carbon atom to which they are attached respectively represent a 5-6 membered heterocyclic group; R₃ represents a trifluoromethyl, a C₁₋₄ alkyl, a C₁₋₄ alkoxy, a trifluoromethoxy or a halogen group; R₄ represents hydrogen, a (CH₂)_qR₇ or a (CH₂)_rCO(CH₂)_pR₇ group; R₅ represents hydrogen, a C₁₋₄ alkyl or a COR₆ group; R₆ represents hydrogen, hydroxy, amino, methylamino, dimethylamino a 5 membered heteroaryl group containing 1 to 3 heteroatoms selected from oxygen, sulphur and nitrogen or a 6 membered heteroaryl group containing 1 to

3 nitrogen atoms; R₇ represents hydrogen, hydroxy or NR₈R₉ wherein R₈ and R₉ represent independently hydrogen or C₁₋₄ alkyl optionally substituted by hydroxy, or by amino; R₁₀ represents hydrogen, a C₁₋₄ alkyl I group or R₁₀ together with R₂ represents a C₃₋₇ cycloalkyl group; m is zero or an integer from 1 to 3; n is zero or an integer from 1 to 3; both p and r are independently zero or an integer from 1 to 4; q is an integer from 1 to 4; provided that, when R₁ and R₂ together with nitrogen and carbon atom to which they are attached respectively represent a 5 to 6 membered heterocyclic group, i) m is 1 or 2; ii) when m is 1, R is not fluorine and iii) when m is 2, the two substituents R are not both fluorine, and pharmaceutically acceptable salts and solvates thereof.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/09722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D241/04 A61K31/496 A61P25/22 C07D401/06 C07D403/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 308 387 A (ANDERS K.K.BJÖRK) 29 December 1981 (1981-12-29) column 1 -column 11; example 35	1,15-18
A	DAVID T. DAVIES: "SYNTHESIS A. BIOLOGICAL ACTIVITY OF A SERIES OF PIPERAZIN-2,3-DIONES" JOURNAL OF ANTIBIOTICS., vol. XLII, no. 3, 1989, pages 367-73, XP002164668 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 page 367; examples 5C,5D	1,15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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- *8* document member of the same patent family

Date of the actual completion of the international search

4 April 2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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